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Oxidative Stress and Parkinson's Disease: New Hopes in Treatment with Herbal Antioxidants

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder due to dopamine deficit in substatia nigra. PD is mainly a sporadic disease with unestablished etiology. However, exposure to environmental toxins, head trauma, inflammation, and free radicals are potential reasons. Recently, the role of oxidative stress in neurological abnormalities, including PD, has been particularly addressed. Antioxidant remedies, particularly herbal antioxidants, have revealed new perspectives of research and therapy as possible preventive and therapeutic approaches for PD. In this paper, we reviewed the recently published papers on the effects of herbal medicines on PD alongside the pathogenesis of PD with regard to oxidative stress.

Keywords: Antioxidant, Degenerative disorder, Herbal medicines, Medicinal plants, Oxidative stress, Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder which is caused by reduction in dopamine level and loss of projecting dopaminergic neurons in striatum and substantia nigra [1]. Dopaminergic impairment in PD leads to alterations in basal glutamatergic synaptic transmission of striatum and plasticity in the medium spiny neurons [1]. PD affects 2% of the population older than 65 years, with 7-10 million individuals affected worldwide [2]. Its symptoms include resting tremor, rigidity of muscles, bradykinesia, and postural and gait impairments [3].

The most cases of Parkinson's disease are sporadic, with undetermined etiology. . However, exposure to environmental toxins, head trauma, inflammation, and free radicals are potential reasons [4, 5]. Remarkable neuroinflammation which is exacerbated by free radicals has been reported in the substantia nigra in the patients with PD [6]. The neurotoxins and cytokines released from the reactive inflammatory cells cause distraction of the projecting dopaminergic neurons in striatum and substantia nigra [6]. Neuroinflammation inhibition in the striatum and substantia nigra has been shown to significantly ameliorate the behavioral deficiency in PD [7].

Recently, special attention has been paid to the role of oxidative stress in neurological abnormalities, including PD. In fact, excessive production of reactive oxidative species (ROS) has been considered as the cause of neuronal death [8, 9].

There is no cure for PD yet, and treatment is mainly symptomatic. The therapies based on a dopamine replacement consist of the use of dopamine precursors; however, substantial adverse effects may appear in long-term usage. Novel pharmacotherapy and cell replacement, before being routinely used in humans, need extensive evaluation [10].

The evidence that mitochondria and ROS as the main neurodegeneration players have caused antioxidant remedies opens new perspectives of research and therapy as possible preventive and therapeutic approaches for PD [11].

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In fact, PD usually starts long before its manifestations appear. Therefore, the diets and medicinal plants with low side effects to prevent them as well as knowledge of the first appearing biomarkers and diagnostic methods to disguise the progressing disease at early stages are important. Medicinal plants with antioxidant activities, which are effective on PD have been recently reviewed [12]. However, this review article only covers the Indian plants. In this paper, we reviewed the recently published papers on the effects of herbal medicines on PD alongside the pathogenesis of PD with regard to oxidative stress.

PATHOGENESIS OF PD

About 50 years ago the dopaminergic defect was suggested as the main neurochemical cause of PD; however, the exact causes of this disease are not clear. About 10% of the patients with PD are estimated to have mutations in selected genes. However, it has further complicated the general picture about the underlying factors of PD [13].

In PD, there is a loss of dopaminergic neurons in substantia nigra with projecting nerve fibers residing in the striatum. These neurons play a crucial role in control of voluntary movements, and their degeneration usually leads to debilitating symptoms including resting tremor, muscular rigidity, postural imbalance, and bradykinesia. Aging is an important variable associated with the onset of PD. So that, deficits in the normal cellular function that usually occur with aging increase the vulnerability of dopaminergic neurons [14].

There is no single causative factor to identify sporadic PD. In fact, a multi-factorial nature contributes to the process of nigral cell death, of which mitochondrial dysfunction and elevated levels in formation of ROS are the most important mechanisms [15]. Another factor which may contribute to the neuronal loss underlying PD is neuro-inflammation which in turn increases the ROS and exacerbates PD. The inflammatory response associated with the cell loss in the dopaminergic nigrostriatal tract and the role of immune mechanisms, which are associated with oxidative stress, are being increasingly addressed as important factors in the pathogenesis of PD [13].

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The Role of Free Radicals in PD

Although familial forms of PD have been described, ROS is likely the main underlying mechanism in both genetic and idiopathic cases of PD, leading to cellular dysfunction of dopaminergic neurons. In this regard, the substantia nigra of PD patients contains higher levels of oxidized lipids, DNA and proteins as well as lower levels of glutathione (GSH) [16].

Oxidative stress is potential when there is an imbalance between ROS production and cellular antioxidant activity [17, 18]. The major sources of ROS which cause oxidative stress and deficit in nigral dopaminergic neurons seem to be mitochondrial dysfunction, neuroinflammation and dopamine metabolism [8].

Mitochondria are the main cellular source of free radicals and have a crucial role in oxidative phosphorylation and electron transport [19]. Mitochondria are also involved in calcium homeostasis and regulation and instigation of cell-death pathways. Hence, there is a complex interaction between mitochondria function and other parts of cellular machinery which affects cell survival. Notably, mitochondrial dysfunction is not detected in all patients with PD. However, this factor may have a critical contribution in the future treatment [20].

Opening of the mitochondrial permeability transition pore is a process which usually occurs under oxidative stress, leading to collapse of the mitochondrial membrane potential. Oxidative stress and mitochondrial dysfunction cause activation of apoptotic pathways in response to pro-apoptotic molecules. Mitochondrial dysfunction causes impairment of energy metabolism which in turn renders the cells vulnerable to 'excitotoxicity'. This excitotoxicity increases ROS generation which in turn increases cellular injury [8]. Mitochondrial dysfunction through increasing oxidative stress induces damage to lipids, DNA and proteins and decreases the levels of intrinsic antioxidants [16].

Higher plasma level of 8-hydroxydeoxyguanosine has been reported in patients with PD than in controls. More importantly, increased serum uric acid level, which is a potent antioxidant, is associated with a lower risk of PD [21].

THE ROLE OF DOPAMINE IN INDUCTION OF OXIDATIVE STRESS

Although the symptoms of PD can be controlled by drugs such as levodipa, the benefits of these drugs usually diminish or become less consistent over time. Levodopa is the most effective medication for PD. It passes into the brain and is converted to dopamine. Levodopa is usually used in combination with carbidopa or benserazide which reduce the metabolism of levodopa outside the brain [22].

As already mentioned, the oxidative stress is one of the main causes of cellular dysfunction and PD patients have high levels of oxidized lipids, proteins and DNA in their substantia nigra, as well as low level of reduced GSH. Due to the presence of ROS-generating enzymes like monoamine oxidase and tyrosine hydroxylase, the dopaminergic neurons are prone to oxidative stress. The major sources of this oxidative stress are dopamine quinone which is produced during dopamine metabolism. In this regard, excess cytosolic dopamine is readily oxidized, producing dopamine quinone. Dopamine quinone is able to modify some of proteins such as DJ-1, UCH-L1 and α-synuclein whose dysfunctions have been shown to be associated with dopamine pathophysiology. α-Synuclein permeabilizes the vesicle membrane, causing leakage of dopamine into the cytosol, which inducesdopamine quinone generation [16]. Moreover, dopamine quinone-modified α-synuclein is able to inhibit normal degradation of other proteins. Furthermore, dopamine quinone species are able to modify the cellular molecules such as protein cysteinyl residues and GSH with normal functions being crucial for cell survival. Dopamine quinone induces the conversion of α-synuclein to cytotoxic form, as well [23].

DJ-1 and UCH-L1 have a cysteine residue which is crucial for their activities. The oxidative modification of their cysteine has been reported in PD patients [24]. Dopamine quinone also can lead to dysfunction of mitochondria and inactivation of tyrosine hydroxyalase and dopamine transporter [16]. Furthermore, the proteins that assist in protein folding in endoplasmic reticulum, including protein disulfide isomerase-5 and ER-60/GRP58/ERp57, are also modified by dopamine quinine [22]. Dopamine quinone also induces proteasomal inhibition leading to apoptosis of the cells [25]. Moreover, dopamine quinone is able to cyclize and become the highly reactive aminochrome. In this form the redox-cycling can lead to depletion of cellular nicotinamide adenine dinucleotide phosphate (NADPH) and generation of superoxide, and ultimately it may polymerize to form neuromelanin which exacerbates the neurodegenerative process by triggering neuro-inflammation [26]. Neuromelanin is one of the final products of dopamine oxidation and is accumulated in the nigral region. Furthermore, during dopamine metabolism by monoamine oxidase, hydrogen peroxide is also generated which is converted to the highly reactive hydroxyl radical in the presence of transition metal ions, inducing oxidative stress [16].

Dopamine has been shown to cause selective toxicity to dopaminergic terminals proportional to the levels of dopamine oxidation and quinone-modified proteins [27]. Cysteinyl-catechol derivatives also are found in higher than normal levels in postmortem nigral tissues of patients with PD, suggesting cytotoxic nature of dopamine oxidation [16].

The toxic nature of dopamine oxidation suggests that plant antioxidants may have preventive and/or curative effect on PD.

ANTIOXIDANTS AS A TREATMENT STRATEGY OF PD

Coenzyme Q10 (CoQ10) is an antioxidant which acts as a potent electron transporter for mitochondrial complexes I and II. CoQ10 levels are low in mitochondria of patients with PD. The ratio of oxidized CoQ10 to reduced one is higher in PD patients than in controls, representing higher oxidative stress in PD patients [28]. In a randomized placebo-controlled trial, high-dose of CoQ10 (1200 mg/day) in conjunction with α-tocopherol, was capable of slowing the progression of disease [29]. Large clinical trials are now being planned to investigate the potential effects of CoQ10 and other antioxidants as disease-modifying agents. Resveratrol which is a polyphenolic compound in grape skin with antioxidant activity induces expression of genes involved in oxidative phosphorylation and mitochondrial biogenesis. It is able to protect 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-induced dopaminergic neuron injury in mice [30].

The strategies to counteract ROS and oxidative stress have been shown to be effective in most ROS-induced diseases such as cancer [31, 32], diabetes mellitus [33, 34], atherosclerosis [35, 36] and infectious diseases [37, 38], rather than PD and some other neurological diseases [39, 40]. Although there are some encouraging data suggesting that the compounds affecting mitochondrial function and antioxidant level may slow down PD progression, the data from human studies are not enough to arrive at a definite conclusion. In this regard, the results obtained from medicinal plants with antioxidant activity are encouraging [41, 42].

MEDICINAL PLANTS AND THEIR BYPRODUCTS IN PD

Medicinal plants have recently attracted considerable attention due to prevention and treatment of various diseases including PD [42-44]. A lot of medicinal plants and their formulations have been investigated with regard to PD and can be an alternative for drug discovery. The plants and their components presented here are the most promising candidates for new formulations.

1. Acanthopanax senticosus

Acanthopanax senticosus is from the Araliaceae family. The ethanol extract of this plant has been shown to exert protective effect on dopaminergic neurons in rodent models of PD. It also increases dopamine and noradrenaline levels in PD rat model [45]. Sesamin is one of *A. senticosus* components which modulates catalase (CAT), superoxide dismutase (SOD), tyrosine hydroxylase (TH), inducible nitric oxide synthase (iNOS) and interleukin-6 expression in dopaminergic cells against oxidative stress induced by 1-methyl-4-phenylpyridine (MPP) [46, 47].

2. Alpinia oxyphylla

Alpinia oxyphylla Miq. is from Zingiberaceae family. Its dried, ripe seeds and ethanol extract protect against 6-OHDA-induced damage to dopaminergic neurons and PC12 cells in zebrafish [48]. Protocatechuic acid derived from *A. oxyphylla* is effective on PD in animal models. It also inhibits MPTP-induced neurotoxicity in mice and reduces sodium nitroprusside- or hydrogen peroxide-induced cell death in PC12 cells [49].

3. Astragalus membranaceus

Astragalus membranaceus var. mongholicus is from Leguminosae family. Astragaloside IV prepared from this plant prevents MPP+-induced SH-SY5Y cell death by inhibition of ROS production. Astragaloside IV prevents 6-OHDA induced death of dopaminergic neurons in a dose-dependent manner [50]. Astragalus polysaccharides derived from this plant can prevent the toxicity of bendopa caused by free radicals produced by self-oxidation which could promote the development of PD [51].

4. Camellia sinensis

Green tea produced from the leaves of *Camellia sinensis* (Theaceae family) can reduce the risk of PD [52]. It also attenuates 6-OHDA-induced cell death in SH-SY5Y cells. The green tea catechins have also preventive effects on the SH-SY5Y cells and PD in rat model, via inhibition of ROS-nitrogen monoxide (NO) pathway [53]. The main components of catechins include (−)epicatechin gallate, (−)epigallocatechin-3-gallate, (−)epigallocatechin, and (−)epicatechin, all of which catechins have protective activity on PC12 cells with the best effect by (−)epicatechin gallate. (−)Epigallocatechin-3-gallate has been shown, in dopaminergic SHSY-5Y cells, to reduce dichlorodiphenyl-trichloroethane-induced cell death and regulate dopamine transporter through protein kinase C in MPP+ induced PC12 cells [54]. (−)Epigallocatechin-3-gallate is also able to inhibit cell death and iNOS expression in the MPTP-induced mice model of PD [55, 56]. Notably, this plant in various studies has shown high antioxidant activity [57, 58].

5. Cassia obtusifolia, Cassiae semen or Cassia tora

Ethanol extract of *Cassia obtusifolia*, *Cassiae semen* or *Cassia tora* L. (Leguminosae family) protect dopamine neuronal degradation induced by MPTP and are also effective against neurotoxicities induced by 6-OHDA in PC12 cells [59]. Peroxynitrite (ONOO)-toxicity is involved in neurodegenerative and inflammatory diseases such as PD. Alaternin isolated from this plant has potent ONOO-scavenging activity and anti-inflammatory property, which makes it a suitable candidate for PD [60].

6. Chrysanthemum morifolium and Chrysanthemum indicum

Chrysanthemum morifolium Ramat (Asteraceae family) can prevent the cytotoxicity and enhance cell viability in MPP+- induced SH-SY5Y cells [61]. *C. indicum* L. is effective against MPP+ induced damage in SH-SY5Y cells [62]. The positive effects of these plants are not clear in *in vivo* studies.

7. Cistanche deserticola, Cistanche tubulosa and Cistanche salsa

Cistanche deserticola, *Cistanche tubulosa*, and *Cistanche salsa* (Orobanchaceae) have protective activity on dopaminergic neurons of MPTP-induced PD in mice [63]. Echinacoside, isolated and purified from *C. salsa* protects the striatal monoamine neurotransmitters levels from diminution in 6-OHDA-induced lesion in rats. It also has neuroprotective, neurorescue and neurotrophic effects on MPTP-induced mice model of PD [64]. Acteoside, isolated from these plants, has neuroprotective effects against MPTP-induced mice model of PD and rotenone-induced damage of SH-SY5Y cells [65].

8. Cuscuta australis and Cuscuta chinensis

Cuscuta australis and *Cuscuta chinensis* (Convolvulaceae) are able to protect cells from apoptosis induced by MPP+ and salvianic acid in PC12 cells [66].

9. Ergot alkaloids

The ergot alkaloids have antiserotonin, dopaminomimetic, and antiadrenergic activities and have a broad spectrum of pharmacological effects. Ergot alkaloids have sedative effect on the central nervous system and therapeutic effects against migraine, postpartum haemorrhages, and mastopathy [67].

Most of the ergot alkaloids effects seem to result from their actions as partial agonists or antagonists at serotonergic, dopaminergic, adrenergic, and tryptaminergic receptors. These effects depend on the species, agent, tissue, dosage, and physiological conditions. But, some of their actions are not compatible with this view. For example, while the agonistic effects of ergot are apparent at lower concentrations, the action of methysergide on cerebral blood vessels is opposite. In this regard, few rules on structure-activity relationships have emerged for ergot alkaloids. Small amide derivatives of lysergic acid are relatively selective and potent antagonists of 5-HT; however, the amino acid alkaloids mostly are less selective and reveal similar affinities as blocking agents at tryptaminergic and α-adrenergic receptors [68].

Most studies of ergot derivatives and PD have evaluated their effects on dopamine receptors. Ergoline ring has a structural similarity to the endogenous monoamines which can explain the action of these compounds on serotonergic, dopaminergic, and adrenergic receptors. Pergolide, bromocriptine, and lisuride are presently available as oral ergot dopamine agonists. Bromocriptine, which has weak D_1 receptor antagonistic property and D_2 agonist effect, was the first ergoline recommended for PD. Both pergolide and bromocriptine are effective on relieving the symptoms of PD and reducing the on-off fluctuations of the disease. Pergolide which is the synthetic ergoline derivative has a mild D_1 receptor agonistic effect and a long acting agonistic action at D_2 dopamine receptors [67]. Two drugs possess similar efficacy and adverse effects. The efficacy of long acting bromocriptine is the same as the standard bromocriptine; however, the patients need fewer daily doses. Lisuride is a mild D_1 receptor agonist and a potent postsynaptic striatal D_2 receptor agonist. Its anti PD effect is equivalent to that of pergolide and bromocriptine [68].

Lisuride is a water-soluble drug and hence it can be used intravenously. For control of motor fluctuations of PD, lisuride is very effective when administered by continuous infusion. Its parenteral use might be complicated by incidence of psychiatric side effects, probably due to its serotonergic activities [67, 69].

10. Fraxinus rhynchophylla, F. chinensis, F. szaboana, F. sielboldiana

Fraxetin derived from these plants has antioxidant activity, reduces stress proteins, and is able to prevent the apoptotic death of

dopaminergic cells mediated by oxidative stress caused by rotenone in SH-SY5Y cells [70]. Liriodendrin and esculin, extracted from *F. sielboldiana* have anti-apoptotic effects on dopamine or MPP+-induced cytotoxicity in SH-SY5Y cells [71, 72].

11. Gastrodia elata

The ethanol extract of *G. elata* (Orchidaceae) possesses protective activity against MPP+-induced cytotoxicity on dopaminergic SH-SY5Y cells [73]. Vanillyl alcohol, a potent component of this plant, is able to protect dopaminergic MN9D cells through modulating the apoptotic process and antioxidant activity, against MPP+-induced apoptosis. Therefore, it is a potential candidate for management of neurodegenerative complications such as PD [74].

12. Ginseng

Ginseng is a deciduous perennial shrub of any one of the 11 species of slow-growing plants belonging to the genus Panax of the family Araliaceae. In fact, ginseng is a variety plants, mainly Korean or Asian ginseng (Panax ginseng), American ginseng (Panax quinquefolius), and Siberian ginseng (Eleutherococcus senticosus). Panax ginseng is an important plant which has long been used in traditional Chinese medicine for treatment of weakness and fatigue [75].

Ginseng grows in eastern Asia and North America, typically in cooler climates. Fleshy root of ginseng requires about 5 years of cultivation to reach maturity. Traditionally, the wild root was consumed to strengthen, rejuvenate, and vitalize the entire body. Korean ginseng is more suitable for older people and men. Ginseng is believed to be an anti-aging herb and is a favorable herb due to low toxic effects on the body. Korean ginseng is thought to contain adaptogens which can return the body's system back to normal level. In this regard, ginsengs is used to balance the metabolism, increase energy levels, lower cholesterol, stimulate the immune system, reduce nervousness, and alleviate fatigue. Korean ginseng can stimulate the regeneration of damaged cells, promote detoxification, and enhance the feeling of wellbeing through increasing oxygenation to cells [75, 76].

Ginseng root has anti-aging, anti-cancer, and cardiovascular protective properties which are potentially due to its high level of antioxidant activity. There are 28 kinds of ginsenosides in American ginseng which can improve impairments in movement and loss of neurons in the brain. Ginseng has been shown to be effective in Huntington's disease or other neuropsychological disorders [75, 77].

13. Gynostemma pentaphyllum

The whole plant ethanol extracts of *Gynostemma pentaphyllum* (Cucurbitaceae) have protective effects on 6-OHDA-induced rat model of PD [58]. Gypenosides extracted from *G. pentaphyllum* have neuroprotective activity against dopaminergic neurons in the substantia nigra of mice model of PD against MPP+-induced oxidative injury [78, 79].

14. Hypericum perforatum

The methanol extract of *Hypericum perforatum* L. (Guttiferae) has protective effects against MPTP-induced PD in mice [80]. The extract of *H. perforatum* decreases oxidative stress and enhances gene expression of antioxidant enzymes on rotenone-exposed rats [81]. The whole extract and a flavonoid-rich extract from *H. perforatum* have also neuroprotective effects against trauma induced by H2O2 in PC12 cells. Hyperoside isolated from *H. perforatum* has been shown to protect the PC12 cells from the cytotoxicity induced by tert-butyl hydroperoxide and H2O2 [82],

15. Ligusticum chuanxiong

Ligusticum chuanxiong Hort. (Umbelliferae) and tetramethylpyrazine, one of its active components, are able to decrease the oxidative damage in PD induced by levodopa and improve the dopamine metabolic ratio in the rat striatum [83]. Tetramethylpyrazine is also able to protect dopaminergic neurons against MPTP-induced neurotoxicity in mice model of PD [84].

16. Mucuna pruriens

Mucuna pruriens is from the Fabaceae family and Faboidaceae subfamily. *M. pruriens* is an annual twinning plant in bushes and hedges. It is one of the popular medicinal plants indigenous to tropical countries like India [85].

It is useful in relieving inflammation, delirium, neuropathy, cephalagia, and general debility, nephropathy, dysmenorrhoea, amenorrhoea, ulcers, constipation, elephantiasis, consumption, helminthiasis, fever, and dropsy. The trichomes of pods contain serotonin and mucunain. The trichomes are used as anthelmintic. Seeds contain glutathione, gallic acid, levodopa (4-3, 4-dihydroxy phenylalanine), lecithin, prurenine, prurenidine, glycosides, nicotine, minerals, and dark brown viscous oil [85].

In a double-blinded clinical and pharmacological study the plant was assessed for levodopa pharmacokinetics and clinical effects at two different doses in comparison with standard levodopa/carbidopa. Thirty g *M. pruriens* preparation caused shorter latencies as compared to peak levodopa plasma concentration and considerably faster onset of effect. Mean time was 37 min (21%) longer with 30 g *M. pruriens* than with levodopa/carbidopa; peak levodopa plasma concentration was 110% higher and the area under the curve was 165.3% larger. There was no significant difference in tolerability or dyskinesia [86]. The longer action and rapid onset without increase in adverse effect suggest that *M. pruriens* seed powder with natural source of levodopa possibly has advantages over conventional levodopa preparations in treatment of PD. In this regard, evaluation of long term efficacy and tolerability in large controlled trials is required.

In an animal model of PD, *M. pruriens* (drug HP-200) was found to be better in comparison to synthetic levodopa. In this study administration of *M. pruriens* at doses of 2.5, 5.0 or 10.0 g/kg/day for 52 weeks significantly increased the dopamine content of the cortex. However, it had no significant effect on dopamine, levodopa, norepinephrine, serotonin or their metabolites in the nigrostriata. The ability of this plant to improve PD symptoms and failure to exert significant effect on dopamine metabolism in the striatonigral tract may suggest a levodopa enhancing effect or that its effect might be due to components other than levodopa [87].

17. Paeonia lactiflora Pall

In traditional Chinese medicine the dried root of *Paeonia lactiflora* (Ranunculaceae) and its principal bioactive component, Paeoniflorin, are widely used for the treatment of neurodegenerative disorders like PD. Paeoniflorin was also able to alleviate the neurological impairment induced by unilateral striatal 6-OHDA lesion in rat model and acidic damage through autophagic pathway [88, 89]. It also attenuates dopaminergic neurodegeneration and neuroinflammation in the mice model of PD by activation of adenosine receptors [90, 91]. Therefore, it could be a good candidate for the treatment of neurodegenerative diseases like PD.

18. Polygala tenuifolia Willd and Polygala sibirica L.

The water extract from the root of Polygala tenuifolia and Polygala sibirica L. (Polygalaceae) are able to prevent toxin-induced neuronal death in the PC12 cells caused by MPP+. Tenuigenin is an active component from *P. tenuifolia* and is able to protect the dopaminergic neurons from inflammation-mediated damage induced by the lipopolysaccharides (LPS) or induced by 6-OHDA in SH-SY5Y cells [92, 93].

19. Polygonum cuspidatum Sieb

The dried root and rhizoma of Polygonum cuspidatum (Polygonaceae) and resveratrol, prepared from this plant are able to increase degradation of α-synucleins in expressing PC12 cell lines, to prevent neurotoxicity induced by human prion protein and to protect SH-SY5Y cells against rotenone-induced apoptosis. They are also able to modulate the markers of apoptotic death in dopaminergic neurons against MPP+-induced oxidative stress. Resveratrol has protective effects on MPTP-induced neuron loss mediated by H2O2 [94, 95] and on dopaminergic neurons from multiple insults in organotypic midbrain slice cultures. It potentiates cytochrome P450 2 d22-mediated protection in paraquat- and maneb-induced PD by attenuating oxidative damage and DA depletion in 6-OHDA-induced rat model [96]. Resveratrol is able to protect the neurons in nigral cells [97]. Pinostilbene, one of the resveratrol derivatives, has also protective activity against 6-OHDA-induced neurotoxicity in SH-SY5Y cells [98].

20. Psoralea corylifolia L.

The aqueous extract of *Psoralea corylifolia* (Leguminosae) has inhibitory effect on dopamine and noradrenaline transporters [99]. The bakuchiol, isolated from *P. corylifolia*, inhibits monoamine transporters and regulates monoaminergic functions. It has dopaminergic protective activity as well as antiparkinsonian-like effects [100].

21. Pueraria lobata Willd and Pueraria thomsonii Benth

Pueraria lobata and *Pueraria thomsonii* (Leguminosae), as well as their active component, puerarin, have protective effects against MPP+-induced apoptosis in SH-SY5Y cells and dopaminergic neurons against 6-OHDA neurotoxicity through upregulation of glial cell line-derived neurotrophic factor. They also are able to inhibit the apoptosis in rat model of PD and regulate the effects of ubiquitin proteasome system [101, 102].

22. Rhodiola crenulata

Dried root and rhizoma of *Rhodiola crenulata* (Crassulaceae) and salidroside, one of its active components, are neuroprotective against MPP+-induced apoptosis in PC12 cells by activating PI3K/Akt and inhibiting the NO pathways [103].

23. Salvia miltiorrhiza Bge

The dried root and rhizoma of *Salvia miltiorrhiza* (Labiatae) and salvianolic acid A, salvianic acid A, and salvianolic acid B, derived from this plant, have protective effects against MPP+-induced neurotoxicity. Salvianolic acid A, through increasing the stress tolerance, is able to protect neurons against H2O2-induced injury. Salvianolic acid B is able to protect PC12 cells against H2O2-induced cytotoxicity and SH-SY5Y cells against MPP- or 6-OHDA-induced apoptosis [104-106].

24. Scutellaria baicalensis Georgi

Scutellaria baicalensis Georgi (Labiatae) and baicalein, one of its flavonoids, have neuroprotective activities in 6-OHDA induced PD. They also have protective effects against rotenone-induced neurotoxicity in isolated rat brain mitochondria and PC12 cells and protective effects against endoplasmic reticulum stress-induced apoptosis on HT22 murine hippocampal neuronal cells through substantial decrease in ROS production [107-109]. Baicalein possesses a neuroprotective effects against MPTP-induced neurotoxicity in mice model of PD and reduces the inflammation-mediated degeneration of dopaminergic neurons by inhibition of microglial activation [110, 111].

25. Tripterygium wilfordii Hook

The extract of *Tripterygium wilfordii* (Celastraceae) protects the dopaminergic neurons from LPS-induced inflammatory damage [112]. Tripchlorolide and Triptolide, isolated from this plant, show neurotrophic and neuroprotective activities on dopaminergic neurons against LPS or MPP+-induced damage through immunosuppressive therapy or inhibition of microglial activation. They also upregulate nerve growth factor synthesis in rat astrocyte cultures and enhance the adeno-virus-mediated gene transfer in mice striatum [113, 114],

26. Vicia faba beans

Vicia faba beans, also known as faba bean, fava bean, broad bean, horse bean, field bean, tic bean or bell bean is a member of Fabaceae (pea) family. Fava beans contain levodopa and are able to control the symptoms of PD, the same as drugs containing levodopa. Fava beans are thought to contain substances other than levodopa and are helpful for PD symptoms. The effect of fava bean lasts longer than that of levodopa medications [115].

The amount of levodopa in the bean is enough to be pharmacologically active in PD. There are some reports indicating that the patients with PD would benefit from *Vicia faba* beans and in some cases the response to the beans might be better than conventional levodopa medications. At single dose the patients with PD having pronounced "on-off" motor oscillations benefited the effects of fava beans. The bean meal causes a longer response, which can be explained by higher plasma concentration. If both legumes and pods are ingested, the beans are relatively rich in protein. The beans could have potential advantages in reducing the off period [116].

Further research is needed to determine the efficacy of fava beans. In western countries, the fava beans are less known; therefore, their properties have been less understood, especially with regard to the levodopa content. It should be noted that various species of fava plants have different amounts of levodopa and the patients cannot be sure to obtain the exact mount. High levels of levodopa can cause nausea and raw fava beans can cause an allergic reaction in some patients [110].

Another consideration is the use of monoamine oxidase inhibitor drugs, including phenelzine, tranylcypromine and isocarboxazide taken with pressor compounds (foods high in tyramine, dopamine and phenylethylamine) which can cause a dangerous increase in blood pressure. The levodopa in fava or in medications can be converted to dopamine in the bloodstream. Favism which is an inherited disease in which the patients lack the enzyme glucose-6-phosphate dehydrogenase (G6PD) should also be considered in patients who eat fava beans. These patients may develop hemolytic anemia. G6PD deficiency is seen mostly among African, Southeast Asian and Mediterranean populations [117].

DISCUSSION AND CONCLUSION

The pathogenesis of PD has not been yet fully understood. There are growing bodies of evidence indicating that oxidative stress and inflammation have important role in PD pathogenesis. This knowledge has enabled us to link the mitochondrial dysfunction and oxidative stress with the pathogenesis of PD. *Substantia nigra* is vulnerable to oxidative damage. The main feature of PD is the loss of dopaminergic neurons in the *substantia nigra* [26].

Levodopa is the most effective medication for PD. It is converted into dopamine and then is metabolized to dopamine quinone which acts as the major source of oxidative stress. It has been shown that dopamine causes selective toxicity to dopaminergic terminals proportional to the levels of dopamine oxidation and quinone-modified proteins Dopamine quinone modifies some proteins such as DJ-1, UCH-L1 and α-synuclein which their dysfunctions have been shown to be linked to dopamine pathophysiology. Moreover, dopamine quinone- modified α-synuclein is able to inhibit normal degradation of other proteins [118]. Furthermore, dopamine quinone species are able to modify the cellular molecules such as protein cysteinyl residues and GSH whose normal functions

are crucial for cell survival [119]. These changes and other events induced by dopamine quinone suggest that plant antioxidants may have protective effect against dopamine toxicity on dopaminergic neurons.

The preventive and treatment strategies that counteract oxidative stress are encouraging in laboratory and animal models of PD. There are also studies suggesting agents that modulating mitochondrial function might be beneficial with regards to PD progression. However, the promising results of neuroprotective compounds in animal models have not been adequately tested in human clinical trials. It should be noted that oxidative stress and mitochondrial dysfunction are not specific to PD pathogenesis. There are a wide variety of other diseases such as cancer [120, 121], diabetes [122, 123], atherosclerosis [124, 125], infections [126, 127] and toxic conditions [128, 129] which are complicated by oxidative stress and treated with antioxidants. Hence, modulation of oxidative stress can help to manage other oxidative stress-related conditions, as well.

Another remarkable point is that PD in humans starts long before its clinical symptoms manifestation. Therefore, preventive measures should be taken to reduce the risk of disease. Hence, the use of antioxidant compounds can be crucial. Antioxidants are a variety of compounds which can scavenge free radicals [130, 131]. However, not all antioxidants have been effective on management of PD and other oxidative stress-induced diseases [132, 133]. In comparison to herbal antioxidants, single antioxidants including vitamins C and E seem to be less effective on rescuing the cells from apoptosis [134]. Further studies are needed to understand the mechanisms underlying the different protective capacities of herbal antioxidants and single antioxidants such as vitamins C and E.

Furthermore, the plants presented in this paper, alongside antioxidant activity, mostly have other compounds effective on PD. Hence, to what extent antioxidants are effective in prevention and treatment of PD should be investigated in clinical trials. If herbal antioxidants are effective per se, most plants with antioxidant activity [135-138] must contribute to treating PD, as well.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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CONTRIBUTIONS

AS, MB, HSh and MRK contributed to the collection of the data and preparation of first draft. AS and MRK edited the last version. All read and confirmed the last version.

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